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Worse long-term survival after off-pump than on-pump coronary artery bypass grafting

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Objective: To determine whether off-pump coronary artery bypass grafting (CABG) is associated with worse long-term survival compared with on-pump CABG. We performed a meta-analysis of adjusted observational studies and randomized controlled trials.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through March 2014. Eligible studies were randomized controlled trials and adjusted observational studies (in which appropriate statistical methods adjusting for confounders had been used) of off-pump versus on-pump CABG that had reported long-term (≥5-year) all-cause mortality as an outcome.

Results: Of 478 potentially relevant studies screened initially, 5 randomized trials and 17 observational studies, enrolling a total of 104,306 patients, were identified and included. A pooled analysis of all 22 studies demonstrated a statistically significant 7% increase in long-term all-cause mortality with off-pump relative to on-pump CABG (hazard ratio, 1.07; 95% confidence interval, 1.03-1.11; $P = .0003$). Although a pooled analysis of 5 randomized trials (1486 patients) demonstrated a statistically nonsignificant 14% increase in mortality with off-pump relative to on-pump CABG (hazard ratio, 1.14; 95% confidence interval, 0.84-1.56; $P = .39$), another pooled analysis of 17 observational studies (102,820 patients) demonstrated a statistically significant 7% increase in mortality with off-pump relative to on-pump CABG (hazard ratio, 1.07; 95% confidence interval, 1.03-1.11; $P = .0004$).

Conclusions: A meta-analysis of 22 studies, enrolling a total of >100,000 patients, showed that off-pump CABG is likely associated with worse long-term (≥5-year) survival compared with on-pump CABG. (J Thorac Cardiovasc Surg 2014;148:1820-9)

See related commentary on pages 1829-31.

Supplemental material is available online.

A Cochrane systematic review[1] published in 2012 of 30 randomized clinical trials did not demonstrate any significant benefit for off-pump compared with on-pump coronary artery bypass grafting (CABG) regarding mortality, stroke, or myocardial infarction. In contrast, Møller and colleagues[1] observed, in a pooled analysis of 17 trials,[2-18] better late (>30-day) survival in the group of patients undergoing on-pump CABG with cardiopulmonary bypass and cardioplegic arrest. The follow-up duration of the included trials, however, was <3 years in 12 trials,[3-6,8-14,17] ≥3 but <5 years in 3 trials,[7,16,18] and ≥5 years in only 2 trials.[2,15] The results of our previous 2012 meta-analysis[19] of 14 randomized controlled trials[2,4,6,8,9,14,15,17,18,20-24] suggested that off-pump CABG might increase late (≥1-year) all-cause mortality by 35% compared with on-pump CABG. The follow-up duration of the included trials was <3 years in 8 trials,[4,6,8,9,14,17,22,23] ≥3 but <5 years in 1 trial,[18] and ≥5 years in 5 trials.[2,15,20,21,24] To determine whether off-pump CABG is associated with worse long-term (≥5-year) survival compared with on-pump CABG, we performed a meta-analysis of adjusted observational studies (in which appropriate statistical methods adjusting for confounders had been used) and randomized controlled trials.

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METHODS

Search Strategy

All prospective randomized controlled trials and adjusted observational comparative studies of off-pump versus on-pump CABG that had reported long-term (≥5-year) all-cause mortality were identified using a 2-level search strategy. First, databases, including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched through March 2014 using Web-based search engines (PubMed and OVID).

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
HR = hazard ratio
PS = propensity score
RR = risk ratio

Second, relevant studies were identified through a manual search of secondary sources, including the references of the initially identified studies, and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and additional analysis. The text keywords included "off-pump"; "long-term" or "late"; and "mortality," "death," "deaths," "survival," "outcome," "outcomes," or "follow-up."

Study Selection and Data Abstraction

Studies considered for inclusion had to meet the following criteria: the design was a prospective randomized controlled clinical trial or prospective or retrospective adjusted observational comparative study (in which appropriate statistical methods adjusting for confounders had been used); the study population was patients undergoing CABG; the patients had been assigned to off-pump versus on-pump CABG; and the main outcomes included long-term all-cause mortality. We defined long-term mortality as death during ≥5 years of follow-up in the present analysis. When duplicate reports from the same study were identified, only the most recent publication, or the one with the longest follow-up period, was included. Data regarding detailed inclusion criteria, duration of follow-up, and mortality were abstracted (as available) from each individual study. We extracted a crude (unadjusted) hazard ratio (HR) and 95% confidence interval (CI) of off-pump versus on-pump CABG for mortality from a randomized trial and an adjusted HR (using appropriate statistical methods such as propensity-score [PS] matching, PS stratification, PS-adjusted Cox proportional hazards regression, multivariable Cox proportional hazards regression, and multivariable Poisson regression) from an observational study. When the HR was unavailable from a randomized trial or PS-matched study, the number of deaths in both the off-pump and on-pump groups was used to generate the odds ratio and 95% CI instead of the HR.

Statistical Analysis

We conducted a meta-analysis of the summary statistics from the individual studies. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs in both fixed-effects and random-effects models. Between-study heterogeneity was analyzed using the standard chi-square test. If no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled HR estimates for the remaining studies. To assess the effect of differential adjustment methods among the observational studies on the pooled estimate, the effects of off-pump CABG on mortality were explored separately in the PS-matched studies. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank correlation and linear regression test. All analyses were conducted using Review Manager, version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark), and Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, NJ).

RESULTS

Search Results

Of 478 potentially relevant studies screened initially, 5 prospective randomized controlled clinical trials[2,15,20,21,24] and 17 prospective or retrospective adjusted observational comparative studies[E1-E17] of off-pump versus on-pump CABG reporting long-term (≥5-year) all-cause mortality were identified and included. In total, our meta-analysis included data on 104,306 patients assigned to off-pump or on-pump CABG. The study design and patient characteristics are summarized in Table 1, details of revascularization in Table 2, and graft patency and cardiac events in Table 3. The number of grafts (or distal anastomoses) per patient was reported in 16 studies and was significantly greater for on-pump than off-pump CABG in 8 of the 16 studies (Table 2). The completeness of revascularization was provided in 8 studies, and the index of the completeness of revascularization (or the frequency of complete revascularization) was reported to be significantly greater with on-pump than with off-pump CABG in 6 of the 8 studies (Table 2). In only 1 PS-matched study by Hu and colleagues,[E9] was repeat revascularization, angina, and rehospitalization for cardiac reasons significantly more frequent with off-pump than with on-pump CABG (Table 3).

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Primary Meta-Analysis

A pooled analysis of all 22 studies (104,306 patients) demonstrated a statistically significant 7% increase in long-term (≥5-year) all-cause mortality with off-pump relative to on-pump CABG in the fixed-effects model (HR, 1.07; 95% CI, 1.03-1.11; P for overall effect = .0003; Figure 1). Minimal trial heterogeneity (P for heterogeneity = .09) was present and, accordingly, little difference in the pooled result from random-effects modeling (HR, 1.06; 95% CI, 1.01-1.12; P for overall effect = .03). Although a pooled analysis of 5 randomized controlled trials (1486 patients) demonstrated a statistically nonsignificant 14% increase in mortality with off-pump relative to on-pump CABG (fixed-effects HR, 1.14; 95% CI, 0.84-1.56; P for overall effect = .39; P for heterogeneity = .38), another pooled analysis of 17 adjusted observational studies (102,820 patients) demonstrated a statistically significant 7% increase in mortality with off-pump relative to on-pump CABG (fixed-effects HR, 1.07; 95% CI, 1.03 to 1.11; P for overall effect = .0004; P for heterogeneity = .06; Figure 1).

Sensitivity Analyses

To assess the effect of qualitative heterogeneity in study design and patient selection on the pooled-effect estimate, we performed several sensitivity analyses. First, we excluded the highest weight (43.0%) and largest size (35,644 patients) study by Bakaeen and colleagues[E2] (Continuous Improvement in Cardiac Surgery Program). However, combining the remaining studies still generated statistically significant results favoring on-pump CABG (fixed-effects HR, 1.07; 95% CI, 1.02-1.13; P for overall effect = .003; P for heterogeneity = .07). Second, we sequentially excluded the second highest weight (12.0%) study by Wu and colleagues[E12] (New York State's Cardiac Surgery Reporting System) and the second largest size (12,874 patients) study by Cooper and colleagues.[E3] Without the New York State's Cardiac Surgery Reporting System[E12] (fixed-effects HR, 1.06; 95% CI, 1.02 to 1.11; P for overall effect = .001; P for heterogeneity = .08) or the study by Cooper and colleagues[E3] (fixed-effects HR, 1.07; 95% CI, 1.03 to 1.11; P for overall effect = .0006; P for heterogeneity = .07), the benefit for on-pump CABG in the pooled analysis of the remaining studies

TABLE 1. Trial design and patient characteristics

Study					
Name	**Duration**	**Inclusion criteria**	**Adjustment**	**Follow-up**	**Subgroup**
Randomized controlled trial					
Angelini (BHACAS 1 and 2),[20] 2009	March 1997 to August 1998, BHACAS 1; September 1998 to November 1999, BHACAS 2	Recent MI (<1 mo) and pronounced disease of distal branches of circumflex artery excluded in BHACAS 1 but not BHACAS 2*	—	75.5 ± 20.6 mo, off-pump; 76.7 ± 19.3 mo, on-pump	BHACAS 1*
					BHACAS 2*
					Total*
Karolak,[21] 2007	August 1999 to March 2003	EF ≥ 30%; nonemergency primary isolated CABG	—	5 y (mean, 3.8; IQR, 3.4-4.4)	—
Hueb (MASS III),[15] 2010	—	Primary isolated CABG	—	5 y	—
van Dijk (Octopus),[2] 2007	1998-2000	Primary isolated CABG	—	5 y	—
Puskas (SMART),[24] 2011	March 2000 to August 2001	Elective primary isolated CABG for multivessel disease	—	Mean, 7.5 y (range, 6.8-8.4)	—
Adjusted observational study					
Brown,[E1] 2008	January 2000 to June 2004	Nonemergency isolated CABG	Multivariable CPHR	6 y (median, 4.1)	—
Bakaeen (CICSP),[E2] 2013	October 1997 to April 2011	Primary isolated CABG	PS matching	Median, 6.68 y (IQR, 3.72-9.35)	—
Cooper,[E3] 2009	January 1997 to March 2007	Primary isolated CABG	PS-adjusted CPHR	10 y	White
					Black
					Total
Di Mauro,[E4] 2007	November 1994 to December 2001	Isolated CABG for multivessel disease	PS matching	7.5 ± 1.9 y	—
Filardo,[E5] 2011	1997-2008	Isolated CABG	PS-adjusted CPHR	10 y	—
Fu,[E6] 2009	1999-2005	Isolated CABG	PS-adjusted CPHR	57.96 ± 23.46 mo	Men
					Women
					Total
García Fuster,[E7] 2013	January 1995 to June 2011	Elective primary isolated CABG	PS matching	77 ± 53 mo, off-pump; 126 ± 54 mo, on-pump	—
Gorki,[E8] 2010	January 1999 to September 2008	EF ≤ 30%; isolated coronary disease	PS matching	10 y (median, 44 mo; range, 0-120, off-pump; median, 64.8 mo; range, 0-120, on-pump)	—
Hu,[E9] 2010	1999-2006	Isolated CABG	PS matching	8 y (mean, 4.5)	—
Locker,[E10] 2013	1993-2009	Primary isolated CABG for multivessel disease	Multivariable CPHR	7.6 ± 4.6 y	—
Murzi,[E11] 2012	April 1996 to December 2009	Isolated CABG for left main disease	PS matching	10 y (50.5 ± 31.2 mo, off-pump; 54.4 ± 34.1 mo, on-pump)	—
Wu (NY CSRS),[E12] 2012	July-December 2000	Isolated CABG	PS matching	Median, 7.2 y (IQR, 7.0-7.4)	—
Raja,[E13] 2013	January-December 2002	Isolated CABG for multivessel disease	PS matching	10 y	—
Robertson,[E14] 2013	January 1997 to June 2003	Primary isolated CABG	PS matching	Median, 5.9 y	—
Sarin,[E15] 2011	January 1996 to September 2008	Isolated CABG	PS-adjusted CPHR	10 y	—
Dalén (SWEDEHEART),[E16] 2013	1998-2008	CABG in Sweden	PS matching	Mean, 7.1 y; 362,254 pt-y	—
Synnergren,[E17] 2008	1995-2004	Isolated CABG	Multivariable Poisson regression	5.0 ± 2.8 y (range, 0.5-10.5)	—

DM, Diabetes mellitus; *BHACAS*, Beating Heart Against Cardioplegic Arrest Studies; *MI*, myocardial infarction; *EF*, ejection fraction; *CABG*, coronary artery bypass grafting; *IQR*, interquartile range; *MASS*, Medicine, Angioplasty, or Surgery Study; *SMART*, Surgical Management of Arterial Revascularization Therapies; *CPHR*, Cox proportional hazards regression; *CICSP*, Continuous Improvement in Cardiac Surgery Program; *PS*, propensity score; *NY CSRS*, New York State's Cardiac Surgery Reporting System; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies; *pt-y*, patient-years. *Data from Angelini et al.[3]

was still statistically significant. In general, exclusion of any single study from the analysis did not substantively alter the overall result of our analysis (Figure 2). Additionally, pooling 10 PS-matched studies[E2,E4,E7-E9,E11-E14,E16] (56,028 patients) did not substantially change the pooled estimate (fixed-effects HR, 1.05; 95% CI, 1.004 to 1.09; P for overall effect = .03; P for heterogeneity = .51).

Publication Bias

To assess the publication bias, we generated a funnel plot of the logarithm of the effect size (HR) versus the precision (reciprocal of the standard error) for each study (Figure 3). No evidence was found of a significant publication bias (2-tailed P = .87 and P = .55, adjusted rank correlation and linear regression test, respectively).

TABLE 1. Continued

Off-pump				On-pump			
Patients (n)	Age (y)	Women (%)	DM (%)	Patient (n)	Age (y)	Women (%)	DM (%)
100	62.2 ± 9.6	18.0	19.0	100	61.7 ± 8.6	21.0	14.0
100	63.8 ± 8.5	18.0	32.0	101	61.2 ± 9.2	14.9	29.7
200	63.0 ± 9.1	18.0	25.5	201	61.4 ± 8.9	17.9	21.9
149	62.2 ± 10.0	18.8	29.5	150	63.7 ± 10.0	20.0	36.0
155	61	22	29	153	59	20	27
142	61.7 ± 9.2	33.8	9.2	139	60.8 ± 8.8	29.5	16.5
98	62.5 ± 9.5	22.4	32.7	99	62.2 ± 11.1	23.2	33.3
733	—	28.1	—	778	—	25.1	—
8911	63.9 ± 9.3	0.9	39.3	26,733	63.9 ± 8.9	1.0	40.1
4970	63.7 ± 11.2	28.8	33.2	5871	62.9 ± 10.6	25.4	33.9
1086	60.4 ± 11.7	45.7	47.0	947	59.6 ± 11.1	38.2	46.7
6056	63.1 ± 11.4	31.9	35.7	6818	62.4 ± 10.7	27.2	35.7
862	63.9 ± 9.5	16.5	23.5	862	64.2 ± 9.1	17.9	23.5
732	64.9 ± 10.8	31.4	33.2	7349	64.4 ± 10.7	27.6	34.7
2007	60.35 ± 9.36	0	24.7	2460	59.61 ± 7.69	0	23.4
403	62.90 ± 8.18	100	31.5	489	60.74 ± 6.94	100	32.9
2410	60.78 ± 9.22	16.7	25.9	2949	59.80 ± 7.58	16.6	25.0
250	66 ± 9	22.0	41.6	250	64 ± 9	18.8	33.6
346	66.5 ± 10.6	20.8	50.0	346	64.7 ± 11.0	23.7	42.8
2088	—	—	—	2088	—	—	—
366	—	—	—	8256	—	—	—
548	65.7 ± 9.3	19.9	20.8	548	66.2 ± 8.7	19.2	20.6
2631	67.7 ± 11.0	29.8	31.6	2631	67.7 ± 10.7	29.3	30.9
307	62.3 ± 11.8	28.7	35.2	307	62.6 ± 7.9	31.3	32.2
308	63.5 ± 10.6	25.3	27.6	308	62.7 ± 10.6	27.3	26.6
540	82.9 ± 2.8	45.9	28.0	397	82.3 ± 2.4	44.6	27.2
2852	Mean, 65.4	26	18	2852	Mean, 66.1	25	20
947	64 ± 10	27.0	17.8	8461	66 ± 9	21.1	20.4

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TABLE 2. Details of revascularization

Study	Subgroup	Graft/patient (n) Off-pump	Graft/patient (n) On-pump	Graft/patient (n) *P* value	Index of completeness of revascularization Off-pump	Index of completeness of revascularization On-pump	Index of completeness of revascularization *P* value
Randomized controlled trial							
Angelini (BHACAS 1 and 2),[20] 2009	BHACAS 1*	Median, 2 (range, 1-4)	Median, 2 (range, 1–4)	.3	—	—	—
	BHACAS 1 and 2†	≥3 grafts in patients of 45.0%	≥3 grafts in patients of 56.2%	NS	—	—	—
Karolak,[21] 2007	—	Anastomosis; median, 2.8 ± 0.9	Anastomosis; median, 3.0 ± 0.9	.06	—	—	—
Hueb (MASS III),[15] 2010	—	2.49 (anastomosis, 2.60)	2.97 (anastomosis, 3.18)	<.001	—	—	—
van Dijk (Octopus),[2] 2007	—	Anastomosis; median, 2.4 ± 1.0‡	Anastomosis; median, 2.6 ± 1.0‡	.05	—	—	—
Puskas (SMART),[24] 2011	—	3.39	3.40	—	1.01	1.00	—
Adjusted observational study							
Brown,[E1] 2008	—	3.0	3.3	<.001	—	—	—
Bakaeen (CICSP),[E2] 2013	—	2.66 ± 1.03 (≥3 anastomoses in patients of 56.3%)	3.18 ± 0.89 (≥3 anastomoses in patients, 79.5%)	<.0001	—	—	—
Cooper,[E3] 2009	—	—	—	—	—	—	—
Di Mauro,[E4] 2007	—	Anastomosis; median, 2.6 ± 0.7	Anastomosis; median, 2.6 ± 0.7	.717	—	—	—
Filardo,[E5] 2011	—	—	—	—	—	—	—
Fu,[E6] 2009	Men	Saphenous and arterial anastomoses, 1.90 ± 0.96 and 1.09 ± 0.52, respectively	Saphenous and arterial anastomoses, 2.75 ± 1.01 and 1.07 ± 0.50, respectively	—	1.1108 ± 0.3188	1.3556 ± 0.3265	<.0001
	Women	Saphenous and arterial anastomoses, 1.90 ± 0.95 and 0.95 ± 0.41, respectively	Saphenous and arterial anastomoses, 2.70 ± 0.95 and 0.94 ± 0.44, respectively	—	1.0544 ± 0.2813	1.2962 ± 0.3564	<.0001
García Fuster,[E7] 2013	—	2.7 ± 1.0	2.8 ± 0.9	.35	—	—	—
Gorki,[E8] 2010	—	3.10 ± 0.88	3.53 ± 1.02	—	—	—	—
Hu,[E9] 2010	—	—	—	—	1.1 ± 0.3 (complete in patients, 87.2%)§	1.3 ± 0.3 (complete in patients, 96.0%)§	<.001
Locker,[E10] 2013	—	—	—	—	—	—	—
Murzi,[E11] 2012	—	2.7 ± 0.7	3 ± 0.7	.001	1 ± 0.3 (complete in patients, 88.3%)	1.1 ± 0.3 (complete in patients, 92.0%)	.001 (.04)
Wu (NY CSRS),[E12] 2012	—	Anastomosis; median, 2.69§	Anastomosis; median, 3.34§	<.001	—	—	—
Raja,[E13] 2013	—	2.91 ± 1.06§	3.4 ± 0.4§	<.01	1.09 ± 0.17§	1.11 ± 0.19§	.87
Robertson,[E14] 2013	—	≥3 Anastomoses in patients, 51.9%	≥3 Anastomoses in patients, 68.5%	.0001	Complete in patients, 79.2%	Complete in patients, 88.3%	.002
Sarin,[E15] 2011	—	—	—	—	—	—	—
Dalén (SWEDEHEART),[E16] 2013	—	2.0 ± 1.0§	3.5 ± 1.0§	<.001	—	—	—

(Continued)

TABLE 2. Continued

Study	Subgroup	Graft/patient (n)			Index of completeness of revascularization		
		Off-pump	On-pump	*P* value	Off-pump	On-pump	*P* value
Synnergren,[E17] 2008	—	—	—	—	Complete in patients, 67.1%	Complete in patients, 82.9%	<.001

BHACAS, Beating Heart Against Cardioplegic Arrest Studies; *NS*, not significant; *MASS*, Medicine, Angioplasty, or Surgery Study; *SMART*, Surgical Management of Arterial Revascularization Therapies; *CICSP*, Continuous Improvement in Cardiac Surgery Program; *NY CSRS*, New York State's Cardiac Surgery Reporting System; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies. *Data from Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. *Circulation*. 2000;102:1530-5. †Data from Angelini et al.[3] ‡Data from van Dijk D, Nierich AP, Jansen EW, Nathoe HM, Suyker WJ, Diephuis JC, et al, Octopus Study Group. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation*. 2001;104:1761-6. §Unmatched patients.

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DISCUSSION

The results of our analysis suggest that off-pump CABG might be associated with worse long-term (≥5-year) survival compared with on-pump CABG. The results from the adjusted observational studies were the most compelling, with data from 102,820 patients in 17 different studies demonstrating a 7% increase in all-cause mortality with off-pump relative to one-pump CABG that was robust in the sensitivity analyses, even after eliminating the highest weight and largest size,[E2] second highest weight,[E12] or second largest size study.[E3] The data from 5 randomized controlled trials were less robust, however, likely owing to the systematic underpowering of these trials in the design phase and, primarily, the small number of enrolled patients (n = 1486). The observed 14% increase (underpowered as reflected by the wide 95% CIs and

TABLE 3. Graft patency and cardiac events

Outcome	Study	Event rate (%)		
		Off-pump	On-pump	*P* value
Graft patency				
	BHACAS 1 and 2,[20] 2009			
	SMART,[24] 2011	89.0*,†	89.4*,†	>.99
		76*,†	83.5*,†	.44
Cardiac mortality				
	Octopus,[2] 2007	0†	1.4†	.24
	Hu,[E9] 2010	5.9‡,§	6.1‡,§	.54
Repeat revascularization				
	BHACAS 1 and 2,[20] 2009	1.5†	1.5†	1.00‖
	MASS III,[15] 2010	6.5†	5.9†	.84
	Octopus,[2] 2007	7.7†	5.0†	.47
	SMART,[24] 2011	2.3†	2.3†	1.0
	Hu,[E9] 2010	9.1‡,§	8.4‡,§	.03
	Raja,[E13] 2013	0.7§	0.7§	1.00
Angina				
	BHACAS 1 and 2,[20] 2009	14.0†	18.9†	.19‖
	MASS III,[15] 2010	11.8†	6.7†	.09
	SMART,[24] 2011	25.6†	11.4†	.09
	Hu,[E9] 2010	28.7‡,§	24.7‡,§	.002
Myocardial infarction				
	BHACAS 1 and 2,[20] 2009	4.0†	4.0†	.99‖
	MASS III,[15] 2010	6.5†,¶	2.0†,¶	.05
	Octopus,[2] 2007	4.9†	6.5†	.62
	Hu,[E9] 2010	3.3‡,§,#	2.8‡,§,#	.22
Rehospitalization for cardiac reason				
	Karolak,[21] 2007	35†	35†	.57
	Hu,[E9] 2010	45.2‡,§	37.5‡,§	<.001
	Raja,[E13] 2013	3.3§	3.6§	.93
	Robertson,[E14] 2013	31.7§	31.9§	.72
	SWEDEHEART,[E16] 2013	51§,**	57§,**	.22

BHACAS, Beating Heart Against Cardioplegic Arrest Studies; *SMART*, Surgical Management of Arterial Revascularization Therapies; *MASS*, Medicine, Angioplasty, or Surgery Study; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies. *Patency rate. †Randomized patients. ‡Per 1000 person-years. §Propensity-score matched patients. ‖Calculated by us. ¶Acute myocardial infarction. #Nonfatal myocardial infarction. **Composite of all-cause mortality and rehospitalization for myocardial infarction, heart failure, or stroke.

Study or Subgroup	log[Hazard Ratio]	SE	Off-pump Total	On-pump Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Rndomized controlled trial						
BHACAS 1&2 2009	0.2185	0.2791	200	201	0.4%	1.2442 [0.7200, 2.1501]
Karolak 2007	0.6924	0.5164	149	150	0.1%	1.9985 [0.7263, 5.4988]
MASS III 2010	0.5064	0.4646	155	153	0.2%	1.6593 [0.6675, 4.1247]
Octopus 2007	0.2877	0.4581	142	139	0.2%	1.3334 [0.5433, 3.2725]
SMART 2011	−0.2581	0.2649	98	99	0.5%	0.7725 [0.4596, 1.2984]
Subtotal (95% CI)			**744**	**742**	**1.3%**	**1.1448 [0.8405, 1.5592]**
Heterogeneity: Chi² = 4.21, df = 4 (P = 0.38); I² = 5%						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.1.2 Adjusted observational study						
Brown 2008	0.3155	0.1361	733	778	1.8%	1.3709 [1.0500, 1.7901]
CICSP 2013	0.0583	0.0278	8911	26733	43.0%	1.0600 [1.0038, 1.1194]
Cooper 2009	0.0738	0.0638	6056	6818	8.2%	1.0766 [0.9500, 1.2200]
Di Mauro 2007	−0.2738	0.1878	862	862	0.9%	0.7605 [0.5263, 1.0989]
Filardo 2011	0.1709	0.0771	732	7349	5.6%	1.1864 [1.0200, 1.3799]
Fu 2009, men	−0.2006	0.3955	2007	2460	0.2%	0.8182 [0.3769, 1.7764]
Fu 2009, women	−0.1385	0.1423	403	489	1.6%	0.8707 [0.6588, 1.1507]
García Fuster 2013	−0.0363	0.2421	250	250	0.6%	0.9644 [0.6000, 1.5499]
Gorki 2010	0.0451	0.1103	346	346	2.7%	1.0461 [0.8428, 1.2986]
Hu 2010	−0.162	0.145	2088	2088	1.6%	0.8504 [0.6401, 1.1300]
Locker 2013	0.2726	0.0812	366	8256	5.0%	1.3134 [1.1201, 1.5399]
Murzi 2012	0.111	0.1653	548	548	1.2%	1.1174 [0.8082, 1.5449]
NY CSRS 2012	0.0953	0.0526	2631	2631	12.0%	1.1000 [0.9922, 1.2194]
Raja 2013	−0.0943	0.1339	307	307	1.9%	0.9100 [0.7000, 1.1831]
Robertson 2013	−0.1208	0.1967	308	308	0.9%	0.8862 [0.6027, 1.3031]
Sarin 2011	−0.265	0.1792	540	397	1.0%	0.7672 [0.5400, 1.0901]
SWEDEHEART 2013	0.0271	0.0619	2852	2852	8.7%	1.0275 [0.9101, 1.1600]
Synnergren 2008	0.069	0.1365	947	8461	1.8%	1.0714 [0.8199, 1.4001]
Subtotal (95% CI)			**30887**	**71933**	**98.7%**	**1.0671 [1.0294, 1.1062]**
Heterogeneity: Chi² = 26.78, df = 17 (P = 0.06); I² = 37%						
Test for overall effect: Z = 3.54 (P = 0.0004)						
Total (95% CI)			**31631**	**72675**	**100.0%**	**1.0681 [1.0306, 1.1069]**
Heterogeneity: Chi² = 31.18, df = 22 (P = 0.09); I² = 29%						
Test for overall effect: Z = 3.61 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						

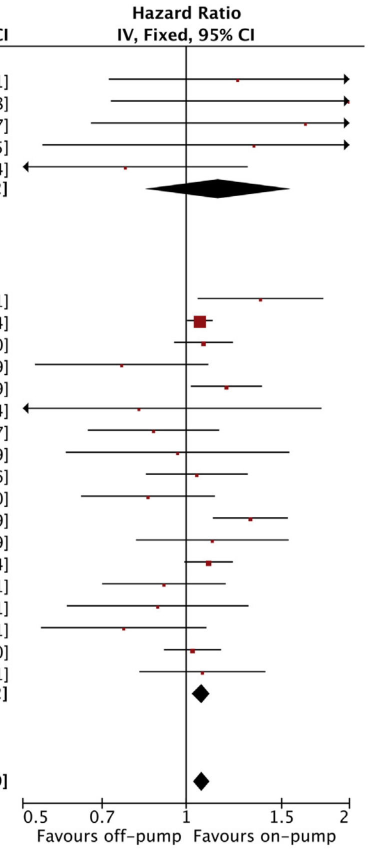

FIGURE 1. Forest plot of hazard ratios for long-term all-cause mortality among patients assigned to off-pump versus on-pump coronary artery bypass grafting. *SE*, Standard error; *IV*, inverse variance; *CI*, confidence interval; *BHACAS*, Beating Heart Against Cardioplegic Arrest Studies; *MASS*, Medicine, Angioplasty, or Surgery Study; *SMART*, Surgical Management of Arterial Revascularization Therapies; *CICSP*, Continuous Improvement in Cardiac Surgery Program; *NY CSRS*, New York State's Cardiac Surgery Reporting System; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies.

lack of statistical significance) in ≥5-year mortality in the patients undergoing off-pump CABG is far lower than the 34% increase in >30-day mortality (risk ratio [RR], 1.34; 95% CI, 1.08-1.67; $P = .009$) and 35% increase in ≥1-year mortality (odds ratio, 1.35; 95% CI, 1.07-1.70; $P = .01$) demonstrated in the recent Cochrane systematic review[1] and our previous meta-analysis,[19] respectively.

In off-pump versus on-pump CABG, the best evidence of a lower number of distal anastomoses[1] and the rate of graft patency[25] could explain the worse long-term survival demonstrated in the present meta-analysis. This is because CABG with complete revascularization improves survival compared with CABG with incomplete revascularization in patients with multivessel disease.[26] The average mean difference in the number of distal anastomoses after off-pump CABG was −0.28 (95% CI, −0.40 to −0.16; $P < .00001$) in the Cochrane meta-analysis[1] of 57 trials (7071 participants). A recent 2014 meta-analysis by Zhang and colleagues[25] of 12 randomized controlled trials (3894 and 4137 grafts performed during off-pump CABG and on-pump CABG, respectively) showed an increased risk of occlusion of all grafts (RR, 1.35; 95% CI, 1.16-1.57; $P < .001$) and saphenous vein grafts (RR, 1.41; 95% CI, 1.24-1.60; $P < .001$) in the off-pump group. However, no significant difference was found in graft occlusion of the left internal mammary artery (RR, 1.15; 95% CI, 0.83-1.59; $P = .407$) or radial artery (RR, 1.37; 95% CI, 0.76-2.47; $P = .298$) grafts between off pump and on-pump CABG. However, our recent 2014 meta-analysis[26] of adjusted HRs (not unadjusted) from 14 observational studies (30,389 patients) demonstrated a statistically significant 37% reduction in follow-up mortality with complete revascularization relative to incomplete revascularization (HR, 0.63; 95% CI, 0.53-0.75; $P < .00001$). Furthermore, the finding of worse long-term survival after off-pump relative to on-pump CABG might be strengthened by the results from another 2013 meta-analysis.[27] The pooled analysis of 12 randomized trials enrolling a total of 11,594 patients demonstrated a statistically significant

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
BHACAS 1&2 2009	1.07	1.03	1.11	3.570	0.0004
Karolak 2007	1.07	1.03	1.11	3.568	0.0004
MASS III 2010	1.07	1.03	1.11	3.573	0.0004
Octopus 2007	1.07	1.03	1.11	3.591	0.0003
SMART 2011	1.07	1.03	1.11	3.689	0.0002
Brown 2008	1.06	1.03	1.10	3.333	0.0009
CICSP 2013	1.07	1.02	1.13	2.966	0.0030
Cooper 2009	1.07	1.03	1.11	3.425	0.0006
Di Mauro 2007	1.07	1.03	1.11	3.772	0.0002
Filardo 2011	1.06	1.02	1.10	3.179	0.0015
Fu 2009, men	1.07	1.03	1.11	3.640	0.0003
Fu 2009Ewomen	1.07	1.03	1.11	3.769	0.0002
Garcia Fuster 2013	1.07	1.03	1.11	3.635	0.0003
Gorki 2010	1.07	1.03	1.11	3.595	0.0003
Hu 2010	1.07	1.03	1.11	3.784	0.0002
Locker 2013	1.06	1.02	1.10	2.934	0.0033
Murzi 2012	1.07	1.03	1.11	3.561	0.0004
NY CSRS 2012	1.06	1.02	1.11	3.182	0.0015
Raja 2013	1.07	1.03	1.11	3.744	0.0002
Robertson 2013	1.07	1.03	1.11	3.686	0.0002
Sarin 2011	1.07	1.03	1.11	3.783	0.0002
SWEDEHEART 2013	1.07	1.03	1.11	3.646	0.0003
Synnergren 2008	1.07	1.03	1.11	3.578	0.0003
	1.07	1.03	1.11	3.613	0.0003

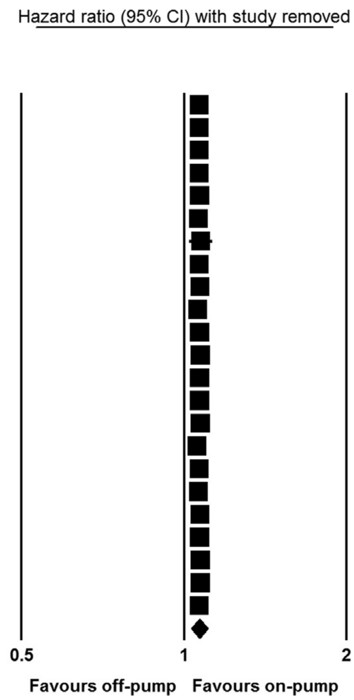

FIGURE 2. One-study-removed meta-analysis of hazard ratios for all-cause long-term mortality among patients assigned to off-pump versus on-pump coronary artery bypass grafting. *CI*, Confidence interval; *BHACAS*, Beating Heart Against Cardioplegic Arrest Studies; *MASS*, Medicine, Angioplasty, or Surgery Study; *SMART*, Surgical Management of Arterial Revascularization Therapies; *CICSP*, Continuous Improvement in Cardiac Surgery Program; *NY CSRS*, New York State's Cardiac Surgery Reporting System; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies.

38% increase in repeat revascularization rates with off-pump relative to on-pump CABG (odds ratio, 1.38; 95% CI, 1.09-1.76; $P = .008$).[27]

Successful performance of off-pump CABG seems likely to depend on initial technical risks more than with on-pump CABG, because, inherently, on a beating heart, performing delicate anastomoses is difficult and the potential degree of revascularization completeness or quality low.[28] Thus, to guarantee surgeon' skill in the assigned technique (off-pump or on-pump CABG), the approach of an expertise-based randomized controlled trial[29] should be used. In the largest size (4752 patients) randomized controlled trial, the CABG Off or On Pump Revascularization Study,[28] expertise was defined as >2 years of experience and the completion of >100 procedures involving the specific technique. Those surgeons who had met these criteria for each type of operation separately were considered to have expertise in both techniques and were allowed to perform both types of CABG during the trial.[28] The investigators of the trial[30] found, at 1 year, no significant differences between the 2 groups in the rate of death (HR, 0.87; 95% CI, 0.58-1.31), nonfatal stroke, nonfatal myocardial infarction, or nonfatal new renal failure requiring dialysis or in the rate of subsequent revascularization procedures. Also, in the second largest size (2370 patients) randomized trial, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients,[31] the study surgeons were required to be established experts in the performance of either off-pump or on-pump CABG and the average number of CABG surgeries performed before the study was 514 off-pump (median, 322) for the off-pump CABG surgeons and 1378 on-pump (median, 578) for the on-pump CABG surgeons. The trial showed no significant differences between off-pump and on-pump CABG with regard to death (HR, 0.88; 95% CI, 0.65-1.18; $P = .38$), stroke, myocardial infarction, repeat revascularization, or new renal replacement therapy within 12 months after surgery.[31] The mid-term and long-term outcomes of these large-size expertise-based randomized trials are expected.

Our analysis must be viewed in the context of its limitations. First, we used data from adjusted observational studies and randomized controlled trials. Although the study design of the randomized trials, which balance both known and unknown confounders across treatment groups, is the least vulnerable to bias, the patients enrolled in them might not be representative of the patients typically seen in clinical practice. However, because the potential biases must be greater for observational studies than for the randomized trials, the results should be always interpreted

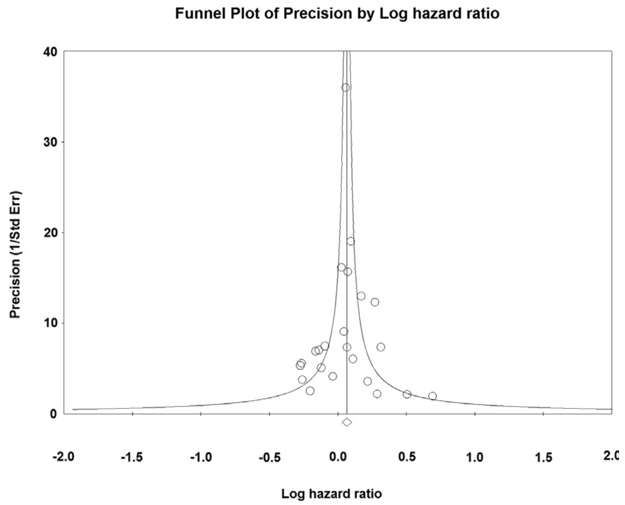

FIGURE 3. Funnel plot of the logarithm of effect size (hazard ratio) versus the precision (reciprocal of the standard error [*Std Err*]) for each study.

with caution when they have been included in meta-analyses.[32] Particular concerns arise in terms of differences between patients in different intervention groups (selection bias). In contrast to randomized trials, it would usually be appropriate to analyze adjusted (ie, attempting to control for confounding), rather than unadjusted, effect estimates.[32] To reduce the effect of treatment-selection bias and potential confounding in observational studies, rigorous adjustment for significant differences in the baseline characteristics of the patients should be conducted. Furthermore, adjusted estimates (not unadjusted) should be pooled in a meta-analysis that includes observational studies. In the present meta-analysis, we strictly abstracted (and then combined in a meta-analysis) exclusive adjusted relative risk estimates (not unadjusted) from the observational studies. Second, our results could have been influenced by a publication bias favoring on-pump CABG. This risk was minimized through an exhaustive search of the available published data. Although the statistical test results did not indicate a publication bias, we clearly had limited power to detect such a bias, given the small number of studies examined.

CONCLUSIONS

We found that, from a meta-analysis of 22 studies enrolling a total of >100,000 patients, off-pump CABG is likely to be associated with worse long-term (≥5-year) survival compared with on-pump CABG. Because a long-term mortality reduction must imply the greatest clinical benefit among patients undergoing CABG, on-pump rather than off-pump CABG should be considered for patients without contraindications to cardiopulmonary bypass. The long-term results of large (>2000 patients) randomized controlled trials, such as the CABG Off or On Pump Revascularization Study,[30] German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients,[31] and Randomized On/Off Bypass[14] study, will render the last judgment for the question of whether to pump or not to pump.

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EDITORIAL COMMENTARY

Should off-pump coronary artery bypass surgery be abandoned? A potential solution

Harold L. Lazar, MD

See related article on pages 1820-9.

In this issue of the *Journal*, in a meta-analysis of 22 studies enrolling more than 100,000 patients, Takagi and coworkers[1] conclude that coronary artery bypass grafting surgery (CABG) performed off-pump (OPCAB) is associated with worse long-term (>5 years) survival than on-pump CABG (ONCAB).[1] The number of grafts performed per patient and the index of completeness of revascularization were significantly greater for ONCAB than OPCAB patients. Furthermore, the need for repeat revascularization, recurrent angina, and rehospitalization for cardiac-related issues were also more frequent in the OPCAB group.

Previous studies have shown a 37% reduction in late mortality in patients undergoing CABG who have had a complete versus an incomplete revascularization.[2] Several studies have reported a higher incidence of incomplete revascularization with OPCAB techniques, and this has been proposed as a mechanism for the decreased long-term survival in these patients.[2-7] OPCAB has also been associated with decreased graft patency, which may be responsible for decreased long-term survival and an increased need for repeated revascularization procedures.[8] The results of the study by Takagi and coworkers[1] are similar to a recent Cochrane pooled analysis of data from more than 80 trials of ONCAB versus OPCAB that shows superior short-term and midterm survival with the ONCAB technique.[9]

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